



# ***Meningococcal Polysaccharide Vaccine Failure in A Patient with C7 Deficiency and A Decreased Anticapsular Antibody Response***

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# Meningococcal polysaccharide vaccine failure in a patient with C7 deficiency and a decreased anti-capsular antibody response

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**Keywords:** complement deficiency, C7, meningococcus, *Neisseria*, vaccine, military

**Abbreviations:** AH50, alternative complement pathway hemolytic assay; CH50, classical complement pathway hemolytic assay; Ig, immunoglobulin; MASP2, mannose binding lectin associated serine protease; MBL, mannose binding lectin; TCCD, terminal complement component deficiency

A 20-year-old male presented with symptoms of meningococcal sepsis and died despite appropriate medical interventions. Blood cultures grew *N. meningitidis* serogroup Y. The patient had received the meningococcal quadrivalent (A,C,W-135,Y) polysaccharide vaccine 15 months previously. Because the patient had a history of meningococcal meningitis at age 10, archived serum was obtained for further analysis. Complement component C7 was found to be deficient and antibody levels to meningococcal polysaccharides were undetectable for two serogroups and low for the infecting serogroup 10 months post-vaccination. This case highlights the fact that some individuals with terminal complement component deficiencies mount an impaired or short-lived response to vaccination with meningococcal capsular polysaccharides and underscores the appropriateness of a more aggressive vaccination strategy in this patient population.

## Patient Presentation

A 10 y old male presented to his pediatrician with fever, headache and body aches. The following day he developed photophobia, neck stiffness, and petechiae. He presented to a hospital emergency room where lumbar puncture showed pleocytosis and Gram negative diplococci. His platelet count was  $94 \times 10^3/\text{mm}^3$ , but prothrombin and activated partial thromboplastin times were normal. He was treated with dexamethasone for 4 d and a total of 7 d of intravenous antibiotics (ampicillin, switched to meropenem because of a rash) and recovered without sequelae. Cerebrospinal fluid cultures grew *Neisseria meningitidis* (serogroup not specified). A CH50 level performed 1 y later was normal (40 U/mL, reference range 31–66).

At age 19 he received the tetravalent polysaccharide meningococcal vaccine when he joined the military. Fifteen months after vaccination he presented to the local military clinic with a 1 d history of fevers; chills; aching in the muscles of his legs, upper back and neck; and a pounding frontal headache with light sensitivity. At this initial clinic visit he was diagnosed with a probable viral syndrome, prescribed ibuprofen, and excused from duty for the day. About 8 h later he developed nausea and vomiting and a generalized purplish macular rash. His roommate called the clinic and reported that the patient said he felt “like he

did when he had meningitis.” The patient was taken immediately to an emergency room.

On arrival he was in respiratory distress, prompting endotracheal intubation. Admission labs showed a white blood cell count of  $5.2 \times 10^3/\text{mm}^3$ , platelet count  $23 \times 10^3/\text{mm}^3$ , creatinine 2.42 mg/dL, prothrombin time 31.6 sec, activated partial thromboplastin time 131.9 sec and arterial pH of 7.20. He was started on several broad spectrum antibiotics, including ceftriaxone, and dexamethasone. His CH50, drawn while he was in the throes of sepsis, was  $< 10$  U/mL; C3 was low at 62 mg/dL (normal 82–235) and C4 was low at 10 mg/dL (normal 16–70). Despite pressor support, transfusions of fresh frozen plasma and hemodialysis, he expired due to disseminated intravascular coagulation and intracranial hemorrhage on hospital day 6. Blood cultures grew *N. meningitidis* at 24 h, which was subsequently shown to be serogroup Y.

Serum collected while in good health (routinely archived upon joining the military and periodically thereafter) was obtained from the Armed Forces Health Surveillance Center repository and assayed for complement levels as follows:

C6: 10.4 mg/dL (reference range 7.1–12.8);

C7: undetected (reference range 4–11 mg/dL);

C8: 19.8 mg/dL (reference range 10.7–24.9);

C9: 31 mg/dL (reference range 6–29).

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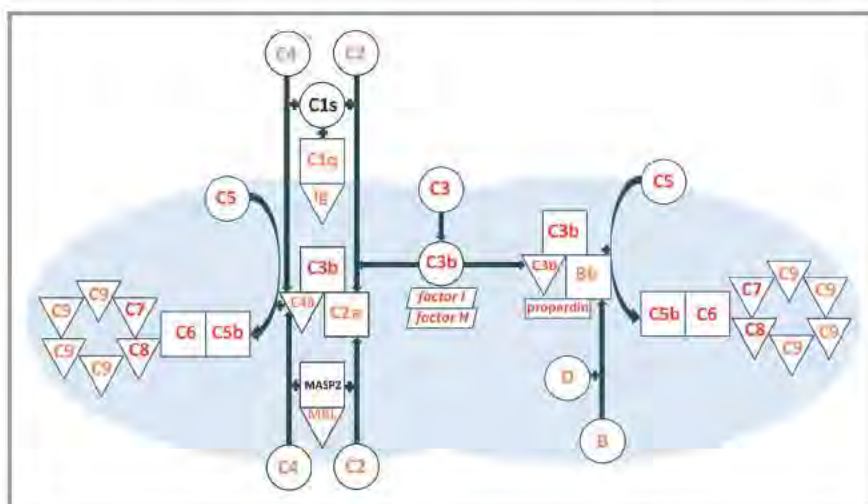


group A capsule: 3.5 µg/mL;  
group C capsule: < 0.5 µg/mL;  
group Y capsule: 0.8 µg/mL;  
group W 135 capsule: < 0.5 µg/mL.

**REFERENCES**

Deficiencies of various components and regulatory proteins of the classical (IgG,<sup>8</sup> C1q,<sup>9</sup> C2,<sup>9</sup> C4<sup>10</sup>) and alternative (properdin,<sup>11</sup> factor D,<sup>12</sup> and factor B<sup>9</sup>) complement pathways predispose to meningococcal disease. Defects of the classical pathway can be compensated for by the alternative pathway and, once an antibody response has developed, vice versa (Fig. 1). Recurrent meningococcal disease is therefore less likely with these deficiencies,<sup>9</sup> though still occasionally reported.<sup>13</sup>

Serum bactericidal activity (SBA) has long been considered a marker for immunologic protection from meningococcal disease,<sup>28</sup> and an increased meningococcal SBA titer is the standard efficacy end point in meningococcal vaccine trials.<sup>29</sup> However



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this test is performed by adding complement pooled from laboratory animals or from immunocompetent human donors, and would over estimate efficacy in individuals with complement deficiencies who are not able to mount a bactericidal response *in vivo*.<sup>9</sup> Such individuals must rely on other immunologic mechanisms, principally opsonophagocytosis,<sup>30</sup> for immune protection. Anti capsular antibody induced by polysaccharide vaccination has been shown to protect individuals with TCCD,<sup>30</sup> however, the antibody response varies. Biselli et al. found that 11 individuals with homozygous C7, C8 or factor H deficiencies had significantly decreased antibody responses to both group A and group C capsular polysaccharides at 45 d post vaccination vs. 24 controls.<sup>31</sup> Eleven heterozygous individuals appeared to have an intermediate response. Andreoni and colleagues found no significant differences among eight survivors of meningococcal infection with absent CH50 activity, eight heterozygous family members, and three controls at 3–4 weeks post vaccination.<sup>23</sup> Platonov et al. did not find significant differences between 18 patients with C7 or C8 deficiency, 7 of their healthy relatives, or 38 health controls at 54 weeks post vaccination,<sup>32</sup> nor did they find differences 4 y out between 54 complement deficient individuals and controls.<sup>33</sup> Drogari-Apiranthitou and colleagues found trends toward a lower response to group Y 7 y post vaccination in 17 patients with TCCD, but this fell short of statistical significance ( $p = 0.07$ ).<sup>34</sup> Herva et al. reported an individual with low levels of several complement components whose response to group A vaccination was low despite a normal response to a 14 valent pneumococcal polysaccharide vaccine.<sup>35</sup> Taken together, these reports suggest that impaired anti capsular antibody formation is not a uniform feature of TCCD, but is nevertheless significant in some groups.

The anti capsular IgG levels of the patient in this case report, compared with typical responses to meningococcal polysaccharide vaccination, in which the 95% confidence intervals for total antibody to groups A and C remained above 2  $\mu\text{g/mL}$  up to ten years out,<sup>36</sup> appear to be modest for group A, but clearly deficient to group C. His antibodies to group W 135 were undetectable and to group Y were clinically inadequate. This case report represents the earliest time to vaccine failure in a C7 deficient individual in which the infecting serogroup and prior antibody levels are known. Platonov et al. reported on meningococcal disease occurring in a C7 deficient individual at 9 mo post vaccination.<sup>32,37</sup> The serogroup of the infecting organism was not reported, but the individual showed an increase in antibody level to the group C polysaccharide during convalescence, suggesting that this, too, was a vaccine failure. Andreoni et al. reported a case of recurrent meningococcal disease in a C7 deficient patient 2.5 y post vaccination. This patient initially had a good antibody response to the group C polysaccharide. The antibody response at the time of recurrent infection was 0.38  $\mu\text{g/mL}$ , but it is not clear if this was the level when he was first re exposed or reflected consumption due to active infection.<sup>23</sup> Fijen and colleagues documented infection with group Y in C8 $\beta$  deficient individuals at 3.5 and 5 y post vaccination.<sup>38</sup> Based on this experience, they recommended repeat vaccination

after 3 y in individuals with TCCD, a recommendation that was, until recently,<sup>39</sup> reflected in national guidelines.<sup>40</sup>

It has been suggested, based on *in vitro* studies, that anti capsular antibody levels are appropriate surrogate markers for protection in individuals with TCCD, and that levels as low as 1 to 2  $\mu\text{g/mL}$  are adequate for protection.<sup>23</sup> Our case, in which an anti Y antibody level of 0.8  $\mu\text{g/mL}$  5 mo before the terminal infection was not protective, is consistent with this suggestion. Defining a precise minimum protective cutoff is probably not possible due to differences in antibody binding avidities, and anti capsular antibody may underestimate the degree of protection.<sup>30</sup> Nevertheless, this test is readily available and may help identify those with an inadequate response to vaccination.

This case highlights the fact that some individuals with TCCD demonstrate an impaired or short lived response to vaccination with meningococcal capsular polysaccharide, and underscores the appropriateness of a more aggressive vaccination strategy. Current guidelines from the US Centers for Disease Control and Prevention recommend that individuals with complement deficiencies receive a two dose primary series of meningococcal conjugate vaccine followed by boosting every 5 y.<sup>39</sup> Whether or not this will be adequate for this population remains to be seen.<sup>41</sup> Vaccines developed for group B meningococcus based on sub capsular antigens do elicit opsonophagocytic as well as bactericidal activity in normal hosts,<sup>42</sup> and therefore have the potential to induce cross protecting antibodies in individuals with TCCD. Since individuals with TCCD are also susceptible to serogroups not available in vaccines and are less likely to develop cross protection from antibodies to sub capsular antigens that develop as a result of colonization, the use of sub capsular meningococcal vaccines, when they become available, will likely be appropriate. Until such vaccines are available and demonstrate full protection in individuals with TCCD, additional strategies, such as anti biotic prophylaxis or self treatment of prodromal symptoms, seem prudent.

The normal CH50 in this patient at age 11 appears to have been a laboratory error, although some TCCD mutations are associated with subtotal deficiencies that allow for detectable CH50 activity.<sup>43</sup> Unfortunately, no more archived samples are available from this patient to further characterize the precise defect associated with his lack of detectable serum C7. The CH50 test should detect most of those defects that predispose to recurrent meningococcal infection. However, given the high prevalence of complement deficiencies among individuals with sporadic meningococcal disease, the expected increase in this prevalence as the overall incidence of meningococcal disease declines<sup>44</sup> and the possibility of identifying other family members who may be at risk (properdin deficiency is X linked; C7 and other hereditary complement defects are autosomal co dominant<sup>44</sup>), a more thorough workup of the complement system in survivors of meningococcal disease, to include AH50 and/or tests for individual complement components, could be justified.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.



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<b>14. ABSTRACT</b>  This is a case report of a military service member who received the meningococcal vaccine but died of the disease 15 months later. He had terminal complement component deficiency (TCCD), and his anti-capsular antibody levels were inadequate. This case highlights the fact that some individuals with TCCD have an impaired or short-lived response to vaccination with meningococcal capsular polysaccharide, and it underscores the appropriateness of an initial two-dose series.						
<b>15. SUBJECT TERMS</b> complement deficiency, meningococcal, vaccine, military						
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